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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,610	10/08/2004	B. Wesley Trotter	21077YP	4061

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EXAMINER	
JARRELL, NOBLE E	
ART UNIT	**PAPER NUMBER**
1624	
MAIL DATE	**DELIVERY MODE**
07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,610	TROTTER, B. WESLEY	
	Examiner	Art Unit	
	Noble Jarrell	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-5,9,11-21* is/are pending in the application.

4a) Of the above claim(s) *1-3,6-8,10* is/are withdrawn from consideration.

5)☒ Claim(s) *4* is/are allowed.

6)☒ Claim(s) *9 and 11-21* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement..

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The Amendments – After Non-Final Rejection dated 6/15/2007 is acknowledged. Claims 4-5, 9, 11-21 are currently pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 9, 11-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for treatment of gliomas, meningomas, colon cancer, gastric cancer, pancreatic cancer, esophageal cancer, hepatocellular cancer, lung (small cell and non-small cell) cancer, thyroid cancer, breast cancer, ovarian cancer, endometrial cancer, vaginal cancer, cervical cancer, prostate cancer, testicular cancer, renal cell cancer, bladder cancer, osteosarcoma, chondrosarcoma, melanoma, basal cell carcinoma, Hodgkin's disease, and retinal revascularization, does not reasonably provide enablement for the prevention of all cancers and hyperproliferative diseases. Applicants are not enabled for the combination of compounds of claim 21 with any of the second compounds selected from claims 13, 18, and 20. Although examples of each of these compounds are listed on pages 36 to 47 of the specification, applicants provide no working examples that these compounds can be used in combination with the claimed compounds in claim 21. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants are enabled for the treatment of the following neoplasms in mice: gliomas, meningomas, colon cancer, gastric cancer, pancreatic cancer, esophageal cancer, hepatocellular cancer, lung (small cell

and non-small cell) cancer, thyroid cancer, breast cancer, ovarian cancer, endometrial cancer, vaginal cancer, cervical cancer, prostate cancer, testicular cancer, renal cell cancer, bladder cancer, osteosarcoma, chondrosarcoma, melanoma, basal cell carcinoma, Hodgkin's disease (Khandwhala et al. *Endocrine Reviews*, **2000**, *21(3)*, 215-244.). Applicants are enabled for the treatment retinal neovascularization as well. Applicants are not enabled for the prevention of all cancers and hyperproliferative disorders because cancer can be considered a hyperproliferative disorder. Prevention cannot be enabled because Khandwala et al. state "The potency of somatostatin is limited: currently available agents appear to have a maximum IGF-1 suppression capability of 50 %, and a number of the clinical studies to date have employed doses that resulted in significantly less than maximum suppression." If the inhibition is less than 100 %, prevention is not possible.

Combination of claim 21 compounds with a second compound selected from claims 13, 18, or 20 is not enabled. There are no working examples of formulations with these ingredients. What are optimum ratios for the combination of these ingredients? It is unclear whether or not compounds of claim 21 can combine with any of the 12 additional ingredients cited in claims 13, 18, and 20. Related directly to claim 18, Amirkhosravi et al. (*Platelets*, **1999**, *10*, 285-292) has shown that abciximab, a platelet fibrinogen receptor (GP (IIb/IIIa) antagonist, decreases the adherence of platelets to tumor cells, which suggests that binding of melanoma cells is partially mediated by GP IIb/IIIa. Amirkhosravi et al. also state that vascular endothelial growth factor (VEGF) release is decreased when platelets are pretreated with abciximab, due to the decreased level of platelet activation. (page 290, column 2, paragraph 3) Because abciximab decreases VEGF release, cancer growth is inhibited. Thus, Amirkhosravi et al. show that a GP IIb/IIIa antagonist by itself can treat cancer. For applicants to be enabled for the composition, they must show unexpected results from the combination in the treatment of cancer. COX-2 inhibitors have been shown to be effective antineoplastic agents by Midgley et al. (*Expert Opinion in Investigational Drugs*, **2001**, *10(6)*, 1011-1019). Midgley states "COX-2 is upregulated in 40 % of human colorectal cancer

adenomas and 85 % of human colorectal carcinomas. There is also genetic evidence that COX-2 has a direct role in intestinal tumourigenesis, in that activating the COX-2 gene in APC mice dramatically reduces the size and number of polyps." (page 1017, first paragraph under heading titled "4.2.2 Cox-2 Inhibitors") In the next paragraph, Midgley states, "Early trials of novel COX-2 selective inhibitors demonstrate that they retain their antitumourigenic and their therapeutic effect." (page 1017, second paragraph under heading titled "4.2.2 Cox-2 Inhibitors") Does the combination of a COX-2 inhibitor and a compound of claim 21 have an unexpected result in the treatment of any forms of cancer? Since Gp IIb/IIIa antagonists and COX-2 inhibitors show that they have the ability to treat different forms of cancer, applicants are invited to show unexpected results from the combination of these compounds with compounds of claim 21.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compounds of claims 4 and 21 that can treat select cancers and retinal neovascularization. Thus, the claims taken together with the specification imply these compounds can treat a number of cancers and retinal neovascularization.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Although the compounds of claim 4 are novel as is the core structure in claim 21, the art is unpredictable with regard to the patient being treated with these compounds. Khandwala et al. state in section XIII, the summary, pages 236-238, "while some tumors are capable of endogenous IGF production, virtually all are responsive to stimulation by these growth factors. Nevertheless, the limited clinical studies performed to date (mostly with somatostatin analogs) have not been particularly successful. There are several reason for this. The potency of somatostatin is limited: currently available agents appear to have a maximum IGF-1 suppression capability of 50 %, and a number of the clinical studies to date have employed doses that resulted in significantly less than maximum suppression....Mature mice and rats have relatively low levels of circulating IGF-II. This is in contrast to humans whom the circulating levels of IGF-II are actually higher than IGF-I on a molar basis. Thus the modest decrease in IGF-1 concentrations obtained by somatostatin analogs in a mouse model may have more profound effects than in the human." This quote says that human testing is unpredictable. One of ordinary skill in the art cannot readily assume that because these compounds treat tumors in mice and rats, that these compounds will work in humans as well.

(5) The relative skill of those in the art:

One of ordinary skill in the art is a scientist who is knowledgeable about inhibition of IGF-I in mammals.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the treatment of gliomas, meningomas, colon cancer, gastric cancer, pancreatic cancer, esophageal cancer, hepatocellular cancer, lung (small cell and non-small cell) cancer, thyroid cancer, breast cancer, ovarian cancer, endometrial cancer, vaginal cancer, cervical cancer, prostate cancer, testicular cancer, renal cell cancer, bladder cancer, osteosarcoma, chondrosarcoma, melanoma, basal cell carcinoma, Hodgkin's disease, and retinal revascularization..

However, the specification does not provide guidance for the prevention of all cancers and hyperproliferative disorders, as well as the treatment of all cancers. Cancer actually consists of more than 100 different diseases ("What is Cancer / General Definition of Cancer". http://training.seer.cancer.gov/module_cancer_disease/units_whatiscancer1_definition.html, accessed July 12, 2007). Clearly, these compounds are not enabled for all 100, but for the types listed above.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the broad meanings of "cancer" and "hyperproliferation disorder" and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

4. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have named the broad compound of claim 21 formula I, however formula I on page 2 of the specification does not match formula I of new claim 21.

5. Claims 13 and 20 are additionally rejected on the grounds that foreign patents that essential matter is improperly incorporated by reference. "Prenyl-protein transferase inhibitors" (claim 13) and COX-2 inhibitors (claim 20) are two possible second compounds in a composition with compounds of claim 21, hence they can be considered essential material. Examples of these compounds are described in the specification (pages 40-42 and 43-46, respectively). However, in the listing of these compounds, several foreign patents are improperly incorporated by reference. The MPEP states "An incorporation by

reference of essential material to an unpublished U.S. patent application, a foreign application or patent, or to a publication is improper under 37 CFR 1.57(c)." (MPEP 608.01(p))

Specification

6. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

7. The attempt to incorporate subject matter into this application by reference to 10/510610 is ineffective because several foreign patents are improperly incorporated by reference as essential material. The MPEP states "An incorporation by reference of essential material to an unpublished U.S. patent application, a foreign application or patent, or to a publication is improper under 37 CFR 1.57(c)." (MPEP 608.01(p)) Specifically, one foreign patent is listed under the example COX-2 inhibitors (page 45, line 8). Under the definition for "Prenyl-protein transferase inhibitor" (page 40-42), there are several foreign patent documents improperly incorporated by reference as well. Since prenyl-protein transferase inhibitors can be one of the second compounds of compositions of claim 13, they are considered essential material.

8. The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection,

rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

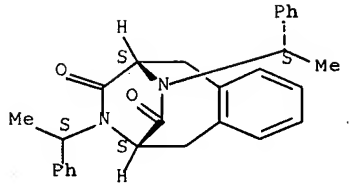
9. The disclosure is objected to because essential subject matter is improperly being incorporated. The MPEP states "An incorporation by reference of essential material to an unpublished U.S. patent application, a foreign application or patent, or to a publication is improper under 37 CFR 1.57(c)." (MPEP 608.01(p)) Specifically, one foreign patent is listed under the example COX-2 inhibitors (page 45, line 8). Under the definition for "Prenyl-protein transferase inhibitor" (page 40-42), there are several foreign patent documents improperly incorporated by reference as well. Since prenyl-protein transferase inhibitors can be one of the second compounds of compositions of claim 13, they are considered essential material. Applicant is invited to look for any additional improper incorporation by references in the disclosure and correct them as well.

Appropriate correction is required.

Allowable Subject Matter

10. Claims 4 and 5 contain allowable subject material.

11. The following is a statement of reasons for the indication of allowable subject matter: the closest prior art of record is a structure taught by Paradisi et al. (*Tetrahedron Asymmetry*, **2000**, *11 (22)*, 4617-4622, based on HCAPlus abstract), which is shown below.



This structure does not read on the claimed compounds because an oxo group is not allowed to be on the ring.

12. Claim 5 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on Monday-Friday from 7:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Noble Jarrell /NJ/

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